REMARKS

Claim Amendments

Claims 116-121 have been canceled.

Claims 16, 21, 23-26, 34-37, 39, 41, 43, 46, 47, 53, 60, 84, 97-102, 109 and 113-115 have been amended.

Claims 16, 21, 34, 41, 47, 53, 60, 84 and 115 have been amended to recite "wherein said ligand is selected from the group consisting of:

i) a ligand having the amino acid sequence of SEQ ID NO:4;

ii) a ligand having an amino acid sequence that is a fragment of SEQ ID NO:4, wherein said fragment is selected from the group consisting of amino acid residues 30-254 of SEQ ID NO:4, amino acid residues 1-202 of SEQ ID NO:4, amino acid residues 30-202 of SEQ ID NO:4, amino acid residues 1-155 of SEQ ID NO:4, amino acid residues 30-155 of SEQ ID NO:4, amino acid residues 1-117 of SEQ ID NO:4, amino acid residues 30-117 of SEQ ID NO:4 and amino acid residues 30 to 95 of SEQ ID NO:4;

iii) a ligand having the amino acid sequence of SEQ ID NO:6;

iv) a ligand having the amino acid sequence of SEQ ID NO:8; and

v) a ligand having the amino acid sequence of amino acid residues 32-101 of SEQ ID NO:8."

Support for this recitation can be found, for example, at page 7, lines 11-19; page 7, line 27 to page 8, line 2; page 19, lines 3-8; page 20, line 23 to page 21, line 3; page 30, line 28 to page 31, line 2; page 44, lines 9-15; and page 72, lines 4-8.

Claims 23, 39 and 46 have been amended to recite "wherein said ligand is selected from the group consisting of:

i) a ligand having the amino acid sequence of SEQ ID NO:4;

ii) a ligand having an amino acid sequence that is a fragment of SEQ ID NO:4, wherein said fragment is selected from the group consisting of amino acid

residues 30-254 of SEQ ID NO:4, amino acid residues 1-202 of SEQ ID NO:4, amino acid residues 30-202 of SEQ ID NO:4, amino acid residues 1-155 of SEQ ID NO:4, amino acid residues 30-155 of SEQ ID NO:4, amino acid residues 1-117 of SEQ ID NO:4, amino acid residues 30-117 of SEQ ID NO:4 and amino acid residues 30 to 95 of SEQ ID NO:4; and

iii) a ligand having the amino acid sequence of SEQ ID NO:6."

Support for this recitation can be found, for example, at page 7, lines 11-19; page 19, lines 3-8; page 20, line 23 to page 21, line 3; and page 72, lines 4-8.

Claims 24, 35, 43 and 97-102 have been amended to recite the phrases "an *in vitro* chemotaxis assay" and "a ligand consisting of amino acid residues 30-254 of SEQ ID NO:4." Claims 43 and 97-102 have also been amended to recite "*signal transduction and/or* a cellular response" as recited in Claims 24 and 35. Support can be found, for example, at page 31, lines 3-29.

Claims 25, 26, 36, 37, 109, 113 and 114 have been amended to alter their dependencies.

The amendments to the claims are supported by the subject application as originally filed. Therefore, this Amendment adds no new matter.

Additional remarks addressing the Examiner's comments and rejections are set forth below with reference to the numbered paragraphs of the Office Action.

Paragraph 3. Anticipated Rejoinder of Claims Pursuant to M.P.E.P. § 821.04

Applicants thank the Examiner for his acknowledgment of the request for rejoinder of Claims 16, 47, 53, 60 and 115. Withdrawn independent process Claims 16, 47, 53, 60 and 115 have been amended in a manner analogous to independent product Claim 21. Therefore, in accordance with M.P.E.P. § 821.04, Claims 16, 47, 53, 60 and 115 should be rejoined and allowed upon allowance of product Claim 21.

Paragraph 5. Information Disclosure Statements

Applicants thank the Examiner for his acknowledgment of consideration of the Supplemental Information Disclosure Statement (SIDS) filed on August 25, 2003. A SIDS is being filed concurrently herewith. Entry and acknowledgment of consideration of the SIDS is respectfully requested.

Paragraphs 13-16. Rejection of Claims 23, 39 and 46 Under 35 U.S.C. § 112, First Paragraph

Claims 23, 39 and 46 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner states that Claims 23, 39 and 46 are drawn to a genus of ligands termed "SExCkine", but that the specification does not appear to provide an adequate description to support the claimed genus. While not agreeing with the Examiner, Claims 23, 39 and 46 have been amended to recite "wherein said ligand is selected from the group consisting of:

i) a ligand having the amino acid sequence of SEQ ID NO:4;

ii) a ligand having an amino acid sequence that is a fragment of SEQ ID NO:4, wherein said fragment is selected from the group consisting of amino acid residues 30-254 of SEQ ID NO:4, amino acid residues 1-202 of SEQ ID NO:4, amino acid residues 30-202 of SEQ ID NO:4, amino acid residues 1-155 of SEQ ID NO:4, amino acid residues 30-155 of SEQ ID NO:4, amino acid residues 1-117 of SEQ ID NO:4, amino acid residues 30-117 of SEQ ID NO:4 and amino acid residues 30 to 95 of SEQ ID NO:4; and

iii) a ligand having the amino acid sequence of SEQ ID NO:6," thereby obviating the rejection.

Paragraphs 19-21. Rejection of Claims 21, 22, 24-27, 34-38, 40-45, 84, 88, 97-109 and 111-114 Under 35 U.S.C. § 112, First Paragraph

Claims 21, 22, 24-27, 34-38, 40-45, 84, 88, 97-109 and 111-114 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner states that the genus of molecules encompassed by the terms "mammalian ligand" and "chemokine ligand" is very large and highly diverse and that the disclosure of two species of ligands does not provide an adequate written description for the claimed genus. (Office Action, page 6, paragraph 21). While not agreeing with the Examiner, independent Claims 21, 34, 41 and 84 have been amended to recite "wherein said ligand is selected from the group consisting of:

i) a ligand having the amino acid sequence of SEQ ID NO:4;

ii) a ligand having an amino acid sequence that is a fragment of SEQ ID NO:4, wherein said fragment is selected from the group consisting of amino acid residues 30-254 of SEQ ID NO:4, amino acid residues 1-202 of SEQ ID NO:4, amino acid residues 30-202 of SEQ ID NO:4, amino acid residues 1-155 of SEQ ID NO:4, amino acid residues 30-155 of SEQ ID NO:4, amino acid residues 1-117 of SEQ ID NO:4, amino acid residues 30-117 of SEQ ID NO:4 and amino acid residues 30 to 95 of SEQ ID NO:4;

iii) a ligand having the amino acid sequence of SEQ ID NO:6;

iv) a ligand having the amino acid sequence of SEQ ID NO:8; and

v) a ligand having the amino acid sequence of amino acid residues 32-101 of SEQ ID NO:8," thereby obviating the rejection.

Paragraphs 22-25. Rejection of Claims 97-102 and 116-121 Under 35 U.S.C. § 112, Second Paragraph

Claims 97-102 and 116-121 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

Specifically, the Examiner rejects Claims 97-102 as being indefinite because without knowing what ligand and what *in vitro* assay, the metes and bounds of the claim cannot be determined. (Office Action, page 6, paragraph 24). While not agreeing with the Examiner, Claims 116-121 have been canceled, and independent Claims 21, 34, 41 and 84 have been

amended to recite particular ligands, as described above. Additionally, Claims 24, 35, 43 and 97-102 have been amended to recite "an *in vitro* chemotaxis assay," thereby obviating the rejection.

Paragraphs 26-34. Rejection of Claims 21-26, 34-46, 97-102, 109, 113, 114 and 116-121 Under 35 U.S.C. § 102(b)

Claims 21-26, 34-46, 97-102, 109, 113, 114 and 116-121 are rejected under 35 U.S.C. § 102(b) as being anticipated by Farber *et al.* (WO 98/44098; cited as Reference AP in IDS). Specifically, the Examiner asserts that Farber *et al.* teach that human STRL33 is bound by HIV as part of the entry of HIV into cells, and that HIV is a ligand of human STRL33. (Office Action, page 7, paragraph 28). The Examiner further asserts that Farber *et al.* teach antibodies and antibody fragments that bind STRL33 and block membrane fusion between HIV and a target cell. (Office action, page 7, paragraph 28). According to the Examiner, given that the antibody taught by Farber *et al.* binds human Bonzo and blocks membrane fusion between HIV and Bonzo, the recited properties of SExCkine binding, inhibition of signal transduction and/or inhibition of cellular responses would be inherent properties of the antibody taught by Farber *et al.* (Office Action, page 7, paragraph 30).

A claim is anticipated under 35 U.S.C. § 102 only if "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil of Cal.*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987) (see also, M.P.E.P. § 2131, pp. 2100-73 *et seq.*, 8th Ed., Latest Rev., May 2004). "Inherency, however, may not be established by probabilities or possibilities; [t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency]. *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q.2d 1949, 1951 (Fed. Cir. 1999) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981)). Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *MEHL/Biophile Intl. Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999) (quoting *In re King*, 801 F.2d 1324, 1326 (Fed. Cir. 1986)).

Farber *et al.* teach that STRL33 (Bonzo) is a functional cofactor for HIV-1 Env-mediated fusion. (Farber *et al.*, page 3, lines 13-18). Farber *et al.* further suggest that "antibodies which bind STRL33 . . . [that are] capable of blocking membrane fusion between HIV and target cells

represent potential anti-HIV therapeutics." (Farber *et al.*, page 3, lines 23-26). Importantly, Farber *et al.* do not actually teach or exemplify any particular anti-STRL33 antibodies that are capable of blocking membrane fusion between HIV and target cells; instead they merely suggest that such an antibody might be produced. As described above, independent Claims 21, 34, 41 and 84 have been amended to recite particular ligands. Farber *et al.* do not expressly teach an antibody or antigen-binding fragment which binds mammalian Bonzo and inhibits the binding of a ligand selected from the group consisting of:

i) a ligand having the amino acid sequence of SEQ ID NO:4;

ii) a ligand having an amino acid sequence that is a fragment of SEQ ID NO:4, wherein said fragment is selected from the group consisting of amino acid residues 30-254 of SEQ ID NO:4, amino acid residues 1-202 of SEQ ID NO:4, amino acid residues 30-202 of SEQ ID NO:4, amino acid residues 1-155 of SEQ ID NO:4, amino acid residues 30-155 of SEQ ID NO:4, amino acid residues 1-117 of SEQ ID NO:4, amino acid residues 30-117 of SEQ ID NO:4 and amino acid residues 30 to 95 of SEQ ID NO:4;

iii) a ligand having the amino acid sequence of SEQ ID NO:6;

iv) a ligand having the amino acid sequence of SEQ ID NO:8; and

v) a ligand having the amino acid sequence of amino acid residues 32-101 of SEQ ID NO:8.

Thus, Farber *et al.* do not expressly teach the claimed antibodies and antigen-binding fragments of the invention.

Moreover, Farber *et al.* also do not inherently teach the claimed antibodies and antigen-binding fragments of the invention. Farber *et al.* suggest an antibody to STRL33 that is capable of blocking membrane fusion between HIV and target cells. As is noted by Farber *et al.*, membrane fusion between HIV and target cells requires the presence of STRL33 and the cofactor CD4. (Farber *et al.*, page 3, lines 15-18). In contrast, Applicants claim an antibody or antigen-binding fragment thereof which binds mammalian Bonzo and inhibits the binding of specified ligands to Bonzo. The Examiner's assertion that the recited properties of inhibition of ligand or SExCkine binding, inhibition of signal transduction and/or inhibition of cellular responses, would be inherent properties of the antibody taught by Farber *et al.* is incorrect.

Evidence that the generic anti-Bonzo antibody suggested by Farber *et al.* would not necessarily or inherently possess the claimed property of inhibiting the binding of the specified ligands is provided by the teachings of (a) Lee *et al.* (Lee *et al.*, *J. Biol. Chem., 274(14)*:9617-9626 (1999), hereinafter Lee *et al.*; Reference AV6 on Supplemental Information Disclosure Statement filed concurrently herewith); (b) Wu *et al.* (Wu *et al.*, *J. Exp. Med., 185(9)*:1681-1691 (1997), hereinafter Wu#1; Reference AT3 on Information Disclosure Statement filed August 27, 2001); and (c) Wu *et al.* (Wu *et al.*, *J. Exp. Med., 186(8)*:1373-1381 (1997), hereinafter Wu#2; Reference AW6 on Supplemental Information Disclosure Statement filed concurrently herewith). These references describe the results of studies of another chemokine receptor, CCR5, which, like Bonzo, is a coreceptor for HIV-1 cellular entry. (*See, e.g.*, abstracts of Lee *et al.*, Wu#1 and Wu#2). As the teachings of these references demonstrate, cellular entry by HIV-1 is a complicated process. Specifically, the HIV-1 envelope (Env) glycoprotein is proteolytically processed from a gp160 precursor to form a mature noncovalent multimeric complex of gp120/41 subunits (Lee *et al.*, page 9617, right column, second paragraph). Binding of gp120 to CD4 triggers conformational changes in Env that enable it to interact with an appropriate coreceptor (e.g., CCR5, Bonzo). (*Id.*) Coreceptor binding is thought to lead to additional conformational changes in Env that result in exposure of the hydrophobic fusion peptide in gp41, which mediates mixing of the viral and cellular membranes. (*Id.*). Thus, coreceptors support both Env binding and induction of conformational changes. (*Id.*)

The Lee *et al.*, Wu#1 and Wu#2 references examined various anti-CCR5 monoclonal antibodies to determine the structural determinants of CCR5 chemokine receptor and coreceptor function. (*See, e.g.*, Lee *et al.*, page 9618, left column, second paragraph). Analysis of these anti-CCR5 antibodies revealed that CCR5 has several immunodominant epitopes on its extracellular face. Specifically, Lee *et al.* demonstrated that monoclonal antibodies to the second extracellular loop of CCR5 were more effective at blocking chemokine binding than Env binding, while monoclonal antibodies to the N-terminal domain blocked gp120 binding, but had little or no effect on CCR5-chemokine interactions. (*Id.; see also,* Lee *et al.*, page 9624, right column). Particular anti-CCR5 monoclonal antibodies (e.g., mAb 3A9) were poor inhibitors of chemokine binding, but inhibited the infection of peripheral blood mononuclear cells (PBMC) by macrophage-tropic HIV-1 *in vitro* (Wu#1, abstract). These teachings demonstrate that antibodies

that inhibit HIV infection do not necessarily inhibit chemokine binding. Accordingly, the teachings of Lee *et al.*, Wu#1 and Wu#2 indicate that the postulated antibody of Farber *et al.*, which binds Bonzo and blocks membrane fusion between HIV and target cells, would not necessarily and inevitably block chemokine function.

As described above, where a claimed composition is not explicitly taught in the prior art, it is inherently anticipated only if the prior art "necessarily functions in accordance with, or includes, the claimed limitations." *MEHL/Biophile Intl. Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999) (quoting *In re King*, 801 F.2d 1324, 1326 (Fed. Cir. 1986)). Clearly, in view of the teachings of distinct binding sites within chemokine receptors for chemokine binding and HIV-mediated functions, the generic antibody suggested by Farber *et al.* would not necessarily inhibit binding of the ligands recited in the claims.

Therefore, in view of the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

Paragraphs 35-43. Rejection of Claims 84 and 121 Under 35 U.S.C. § 103(a)

Claims 84 and 121 are rejected under 35 U.S.C. § 103(a) as being obvious over Farber *et al.* (WO 98/44098; cited as Reference AP in IDS) in view of Jardieu *et al.* (U.S. Patent No. 6,037,454; cited in Form PTO-892 accompanying Office Action dated 09/22/03). The Examiner asserts that although Farber *et al.* do not teach an antibody to Bonzo in a test kit comprising ancillary reagents suitable for detecting the antibody-Bonzo complex, that Jardieu *et al.* teach antibodies to another cell surface receptor, CD11A, which may be packaged in a kit with ancillary agents for detection. (Office Action, pages 9 and 10, paragraphs 39, 40 and 41). According to the Examiner, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the anti-Bonzo antibody taught by Farber *et al.* with one or more ancillary detection reagents, as taught by Jardieu *et al.* (Office Action, page 10, paragraph 42). The Examiner asserts that the person of ordinary skill in the art would have been motivated to produce the antibody in a kit as a matter of convenience, as taught by Jardieu *et al.*, and that in view of the teachings of Farber *et al.* of the anti-Bonzo antibody and Jardieu *et al.* of numerous ancillary reagents, that one would have had a reasonable expectation of formulating the antibody in a kit. (Office Action, page 10, paragraph 42).

As described above, Farber *et al.* do not expressly or inherently teach or suggest the claimed antibodies and antigen-binding fragments. Further, the teachings of Jardieu *et al.* do not teach or suggest the claimed antibodies and antigen-binding fragments. Accordingly, Claims 84 and 121 are not obvious over the cited combination, because neither reference, alone or in combination, teaches or suggests, or provides a reasonable expectation of success in producing, the claimed antibodies.

Paragraphs 44-46. Provisional Rejection of Claims 21-46, 84, 88 and 97-114 Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner has provisionally rejected Claims 21-46, 84, 88 and 97-114 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 21, 28, 31, 34, 197-201, 203, 205 and 206 of copending U.S. Application No. 10/174,293 (Attorney Docket No. 1855.1070-006) for the reasons set forth in the previous Office Action (dated September 22, 2003). The Examiner has further noted Applicants' intention to resolve this issue. (Office Action, paragraph 46). Therefore, if this provisional rejection is the only rejection remaining after entry and consideration of this Amendment, Applicants respectfully request that the Examiner withdraw the rejection and permit the subject application to issue as a patent, in accordance with U.S. Patent Office procedure (see, M.P.E.P. § 804(I)(B), p. 800-19, 8th Ed., Latest Rev., May, 2004).

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Helen E. Wendler

Helen E. Wendler
Registration No. 37,964
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: Dec. 28, 2004